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Treatment of Septic Shock with Human Monoclonal Antibody HA-1A

A Randomized, Double-Blind, Placebo-Controlled Trial

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■ *Objective:* To compare the effectiveness of 100 mg of HA-1A and placebo in reducing the 14-day all-cause mortality rate in patients with septic shock and gram-negative bacteremia in the Centocor: HA-1A Efficacy in Septic Shock (CHESS) trial, and to assess the safety of 100 mg of HA-1A given to patients with septic shock who did not have gram-negative bacteremia.

■ *Design:* Large, simple, group-sequential, randomized, double-blind, multicenter, placebo-controlled trial.

■ *Setting:* 603 investigators at 513 community and university-affiliated hospitals in the United States.

■ *Patients:* Within 6 hours before enrollment, the patients had been in shock with a systolic blood pressure of less than 90 mm Hg after adequate fluid challenge or had received vasopressors to maintain blood pressure. These episodes of shock began within 24 hours of enrollment. A presumptive clinical diagnosis of gram-negative infection as the cause of the shock episode and a commitment from the patients' physicians to provide full supportive care were required.

■ *Measurements:* Blood cultures were obtained within 48 hours of enrollment, and death at day 14 after treatment was recorded. Adverse events occurring within 14 days after enrollment were also tabulated.

■ *Results:* 2199 patients were enrolled; 621 (28.2%) met all enrollment criteria, received HA-1A or placebo, and had confirmed gram-negative bacteremia. Mortality rates in this group were as follows: placebo, 32% (95 of 293) and HA-1A, 33% (109 of 328) ($P = 0.864$, Fisher exact test, two-tailed; 95% CI for the difference, −6.2% to 8.6%). Mortality rates in the patients without gram-negative bacteremia were as follows: placebo, 37% (292 of 793) and HA-1A, 41% (318 of 785) ($P = 0.073$, Fisher exact test, one-tailed; CI, −0.8% to 8.8%).

■ *Conclusions:* In this trial, HA-1A was not effective in reducing the 14-day mortality rate in patients with gram-negative bacteremia and septic shock. These data do not support using septic shock as an indication for HA-1A treatment. If HA-1A is effective in reducing the mortality rate in patients dying from endotoxemia, these patients must be identified using other treatment criteria.

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In a previously conducted trial of human monoclonal antibody HA-1A (1) among 102 patients with gram-negative bacteremia and shock, the all-cause mortality rate 28 days after treatment was reduced from 56% in patients receiving placebo to 33% in those receiving HA-1A (chi-square P value = 0.020). At day 14 in the same group, the mortality rate was reduced from 48% in the placebo group to 24% in the HA-1A group (chi-square P value = 0.012). That was an explanatory trial (1) intended to confirm the findings previously reported with J5 antiserum (2) and was conducted using stringent selection criteria at medical centers expert in conducting clinical trials in sepsis.

An explanatory trial (3, 4) tries to determine if a treatment is beneficial under an ideal or constrained set of clinical circumstances. Other trials, defined as pragmatic or management trials, try to determine the safety and efficacy of a treatment in clinical circumstances as close as possible to those actually or usually encountered. To analyze the effects of commonly used practices to prevent death from frequently encountered diseases, large, simple, randomized trials have theoretical and practical advantages in a management trial (5). To our knowledge, this design has not been used previously in infectious disease and particularly not to study sepsis.

Because death at day 14 in patients with shock and gram-negative bacteremia was not a primary end point in the trial by Ziegler and colleagues (1), we wanted to determine if these results could be reproduced in standard clinical practice at many types of hospitals. We chose a large, simple trial design to test the use of septic shock as an indication for HA-1A treatment.

Methods

The primary objective of the Centocor: HA-1A Efficacy in Septic Shock (CHESS) trial was to compare the effectiveness of 100 mg of HA-1A and placebo in reducing the 14-day all-cause mortality rate in patients with septic shock who had gram-negative bacteremia. The secondary objective was to assess the safety of 100 mg of HA-1A in patients with septic shock who did not have gram-negative bacteremia. To be eligible for enrollment in the trial, patients had to 1) be in shock within 6 hours before enrollment; 2) have gone into shock within the 24 hours before enrollment; 3) have a presumptive clinical diagnosis of gram-negative infection that was judged to have caused the septic shock episode; and 4) have a physician who was committed to providing full, supportive care for the patient and did not con-

Table 1. Final Analysis of the 14-Day Mortality Rate in Patients Who Were Given HA-1A or Placebo and Met all Enrollment Criteria

Group	Placebo	HA-1A	Relative Risk (95% CI)	*P* Value*
	n/n (%)			
Gram-negative bacteremia	95/293 (32)	109/328 (33)	1.02 (0.82 to 1.28)	0.864*
Without gram-negative bacteremia	292/793 (37)	318/785 (41)	1.10 (0.97 to 1.25)	0.073†
All patients	387/1086 (36)	427/1113 (38)	1.08 (0.97 to 1.21)	0.186*

* Fisher two-tailed exact test
† Fisher one-tailed exact test; two-tailed, $P = 0.134$

template withdrawing support. Shock was defined as the presence of either systolic blood pressure less than 90 mm Hg after adequate fluid challenge or use of dopamine, dobutamine, norepinephrine, or epinephrine as vasopressive agents to maintain blood pressure. (Dopamine used at low doses solely to improve renal blood flow was not considered a vasopressive agent.) An adequate fluid challenge was an intravenous infusion of isotonic fluid, colloid, or blood products to restore the effective circulating blood volume.

Excluded were 1) patients younger than 18 years; 2) patients who were pregnant; 3) patients who, because they had rapidly fatal underlying disease, were not expected to live more than 3 months; 4) patients who had an organ or bone marrow transplant within the preceding 6 months; 5) patients with a total leukocyte count less than 500 cells/mm^3; 6) patients with a body surface area burn injury greater than 10% within the preceding 2 months; 7) patients who previously received any antiendotoxin monoclonal antibody; 8) patients with "do not resuscitate" orders; and 9) patients who, at enrollment, were participating in other clinical trials of investigational drugs to treat sepsis or septic shock.

Patients were considered enrolled in the trial after all of the enrollment criteria had been met and a vial of study material was prepared for infusion. Patients were followed for 14 days after infusion.

An independent randomization and interim analysis center prepared a treatment allocation schedule that randomly assigned patients to receive 100 mg of HA-1A or placebo (human serum albumin) in equal proportions. The treatment allocation schedule was assigned in a manner unknown to the sponsor and the participating investigators. The randomization center labeled the study material with sequential vial numbers according to the allocation schedule. The sponsor and the participating investigators could not determine the treatment allocation from a patient's vial number.

Prospective data collected from each patient were limited to 1) conformity with enrollment criteria; 2) gram-negative bacteremia status within 48 hours of enrollment; 3) death at day 14 after enrollment; and 4) the occurrence of spontaneously reported adverse events. The primary efficacy end point was 14-day all-cause death for this specified patient cohort. The primary safety end points were 14-day all-cause death for patients without gram-negative bacteremia and adverse events in all patients infused. No other clinical information was obtained.

We estimated that we needed 1500 patients to detect an 18% proportionate decrease in mortality rate at day 14 after treatment from 49% in the placebo group to 40% in the HA-1A group, with a type I error rate of 0.05 and a power of 90%. Patients who met all enrollment criteria, had gram-negative bacteremia, and received HA-1A or placebo were defined prospectively as the group of primary interest. Because therapy must be instituted immediately in septic shock, patients were treated presumptively before the results of blood cultures were known. Given the difficulty in identifying patients with gram-negative bacteremia on clinical grounds, to accrue the target population of 1500 patients with gram-negative bacteremia, we expected to enroll 3400 to 7500 patients with shock and a presumptive diagnosis of gram-negative infection.

As specified in the protocol, an interim analysis was planned after the data were available for 500 and 1000 patients with shock and gram-negative bacteremia who received HA-1A or placebo. At the interim analysis, the safety and efficacy monitoring committee could recommend stopping 1) if, among patients with septic shock and gram-negative bacteremia, the HA-1A–treated patients had a lower mortality rate at day 14 ($P < 0.010$; Fisher two-tailed exact test) than did patients given placebo; or 2) if, among patients with septic shock without gram-negative bacteremia, the HA-1A–treated patients had a higher mortality rate ($P < 0.1$; Fisher one-tailed exact test) than did patients given placebo. The safety stopping rule was purposefully designed to be sensitive and to serve as an early warning of potential toxicity in patients not expected to benefit from HA-1A treatment.

Results

Figure 1 shows the distribution of patients into those enrolled, those meeting all enrollment criteria, and those in the prospectively specified primary efficacy group (gram-negative bacteremia). Among patients who met all enrollment criteria and who were given HA-1A or placebo, 621 of 2199 (28.2%) had gram-negative bacteremia and 1578 did not.

We stopped the trial at the first interim analysis because the all-cause mortality rate for patients treated with HA-1A who did not have gram-negative bacteremia (42%; 244 of 577) exceeded that of the patients given placebo (38%; 230 of 608) by an amount greater than that

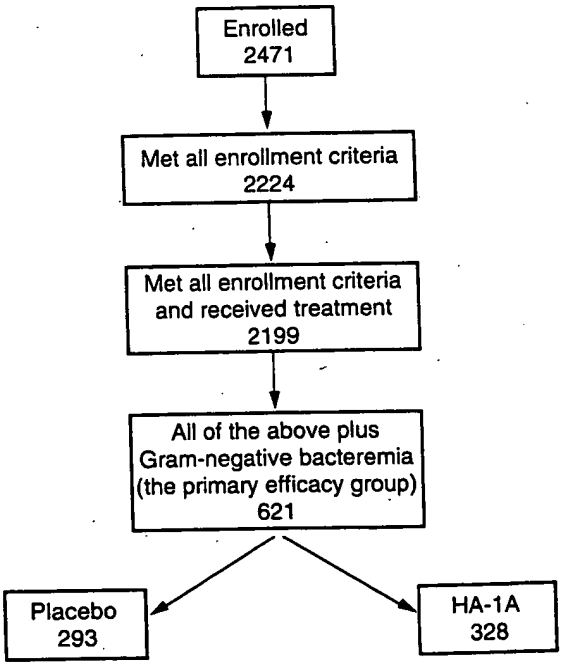

Figure 1. CHESS trial patient distribution.

Table 2. Spontaneously Reported Adverse Events Possibly, Probably, or Definitely Related to Treatment in all Patients Infused with Placebo or HA-1A

Adverse Event	Placebo (n = 1199)	HA-1A (n = 1228)
	n	
Death	1	1
Intravenous site		
Infiltration, phlebitis, or pain	2	1
Chills	0	2
Hot sensations	0	1
Hypotension	25	31
Hypertension	2	3
Dizzy	1	0
Headache	1	0
Abdominal pain	0	1
Diarrhea	1	1
Nausea and vomiting	4	0
Pain in upper quadrant	1	0
Cardiac arrest	1	3
Myocardial infarction	0	1
Hyperbilirubinemia	1	0
Thrombocytopenia aggravated	4	3
Elevated partial thromboplastin time	0	1
Anxiety aggravated	1	0
Positive test results for Coombs hemolytic anemia	1	0
Fever	1	4
Hypoxia	0	3
Rales	0	1
Respiratory distress aggravated	2	2
Acute respiratory distress syndrome	1	0
Wheezing	0	2
Diaphoresis	1	2
Rash	1	4
Flushing	1	1
Sweats	0	1
Neutropenia	1	0

in the prespecified safety stopping rule (P = 0.09; Fisher one-tailed exact test).

Between the performance of the interim analysis and closure of the trial, additional patients were enrolled. These patients were included in the final analysis. Table 1 shows the results for patients with and without gram-negative bacteremia and the results in all patients treated.

The incidence of spontaneously reported adverse events classified as severe or life-threatening was 41 of 1199 (3.4%) for placebo and 41 of 1228 (3.3%) for HA-1A. Table 2 shows events categorized as possibly, probably, or definitely related to infusion of placebo or HA-1A; no previously unreported events were identified. Hypotension was noted in 25 of 1199 patients given placebo (2.1%) and in 31 of 1228 patients receiving HA-1A (2.5%) (P = 0.47). For all treated patients for whom data are available, the incidence of any adverse effect, regardless of severity, was 534 of 1199 (45%) for placebo and 583 of 1228 (47%) for HA-1A treatment. For all treated patients without gram-negative bacteremia for whom data are available, the incidence of any adverse effect, regardless of severity, was 320 of 726 (44%) for placebo and 458 of 1017 (45%) for HA-1A treatment.

Discussion

The results of this trial do not indicate any reduction in 14-day mortality rate with HA-1A treatment in patients with gram-negative bacteremia and septic shock. In the study by Ziegler and colleagues (1), the 14-day mortality rate was reduced from 48% with placebo to 24% with HA-1A in similar patients. Several possible explanations could account for the disparity of these results: 1) The patients treated differed from those treated by Ziegler and colleagues (1) and were less likely to respond to HA-1A treatment; 2) the patients treated with HA-1A were more severely ill than the patients given placebo; 3) the treatment effect of HA-1A was obscured by the difference in mortality rates among the many participating hospitals; 4) the HA-1A used in this trial was inactive or less active than the HA-1A used in the previous trial; 5) the trial was terminated prematurely and its power to detect the expected reduction in mortality rate was low; and 6) the conclusions of the previous trial were incorrect, and HA-1A was not effective in preventing death in patients with gram-negative bacteremia.

The enrollment criteria for the CHESS trial differed from those for the previous trial (1). Shock lasting at least 6 hours and occurring within the 24 hours before enrollment was required. There was no requirement for fever and tachycardia, and there was no provision for enrolling patients with organ failure. The placebo mortality rate in this trial was 32% (95% CI, 27% to 37%) in patients with shock and gram-negative bacteremia and was 48% (CI, 34% to 62%) in the corresponding group enrolled in the previous trial. These data suggest that less severely ill patients were enrolled in the CHESS trial compared with the previous trial. Because HA-1A was most effective in patients with shock and organ failure in the previous trial, and polyclonal J5 antiserum (2) was most effective in patients with "profound" shock, perhaps only the most severely ill patients with shock and organ failure die from sustained endotoxemia and, therefore, benefit from anti-endotoxin immunotherapy.

Because the data collected in this trial were limited by the study design, we could not evaluate the severity of illness in the two treatment groups. Although a similar prognosis in the two groups would be expected because patients were randomly allocated to each treatment and many patients were enrolled, chance differences in the severity of illness in the patients enrolled cannot be excluded. The design of the trial also led to the enrollment of a few patients at many hospitals. We observed a large difference in the mortality rates among hospitals (data not shown). Similar findings have been reported by others (6). If HA-1A was administered more frequently at hospitals with a higher mortality rate and placebo was administered more frequently at hospitals with a lower mortality rate, a reduction in the mortality rate with HA-1A might have been obscured by the difference in mortality rate among hospitals.

The HA-1A used in this trial was tested extensively using in vitro assays to determine if antibody manufacturing variability might have produced inactive or less active material. Results of these studies indicated that the product used in the trial passed all routine release tests and had the same affinity for reference endotoxin. Thus, it seems unlikely that manufacturing variability could account for the results of this trial.

We designed the CHESS trial to detect a reduction in mortality rate in patients with gram-negative bacteremia

and septic shock from 49% in the placebo group to 40% in the HA-1A group, an 18% proportionate reduction. The 49% placebo mortality rate used in the sample size calculation was chosen based on the results of the previous trial (48%), on the mortality results of a large, open-label trial of HA-1A in which the incidence of death in patients with gram-negative bacteremia and shock was 174 of 437 (40%; data on file at Centocor, Inc.), and on a review of the literature. For example, a recent study by Gransden and colleagues (7) found that the mortality rate for patients with gram-negative bacteremia and shock was 52% (CI, 44% to 61%). We expected the mortality rate in the HA-1A group to be higher than that previously reported by Ziegler and colleagues (1) because we knew that severely ill patients with a high frequency of organ failure would be enrolled. Patients with shock and organ failure were frequently enrolled in the open-label trial conducted immediately before the CHESS trial. We determined that 1500 patients would constitute the sample size to detect the difference between 49% and 40% mortality, with an alpha of 0.05 and a power of 90%. Fewer patients were enrolled in this trial because the trial was stopped at the first interim analysis by the safety and efficacy monitoring committee. Only 621 patients with gram-negative bacteremia and septic shock were enrolled and the placebo mortality rate was only 32%. Consequently, the power of this study to detect the 18% proportionate reduction in mortality rate originally hypothesized to occur was about 50%. The CI for the difference in the mortality rate between HA-1A and placebo recipients includes a 6% absolute reduction (or about a 20% proportionate reduction) in mortality rate. Thus, even assuming that no other factors influenced the results, this study was not large enough to exclude clinically meaningful reductions in mortality rate.

The conclusions of the previous trial of HA-1A may have been incorrect and HA-1A may not be effective in patients with sepsis and gram-negative bacteremia. The evidence supporting the efficacy of human antiendotoxin antibody in reducing the mortality rate in patients with gram-negative bacteremia is derived from the two previous randomized, double-blind, placebo-controlled trials reported by Ziegler and colleagues (1, 2). These trials provided similar results that seem to strongly support the efficacy of immunotherapy, but possible sources of error in these studies have been noted by others (8). Given the lack of a suitable animal model to test the efficacy of HA-1A and the results of this trial, additional clinical trials are needed before a definitive determination of the efficacy of HA-1A used in patients with endotoxemia can be made.

Patients dying from endotoxemia are most likely to benefit from antiendotoxin immunotherapy. Developing a reliable method to identify these patients prospectively has been elusive. Any future clinical trials should be explanatory in design and should identify a restricted patient cohort likely to benefit from therapy. For example, fulminant meningococcemia may be an excellent model to test the efficacy of HA-1A. Large, simple trials should be conducted only after the indication for therapy has been precisely defined. Although large, simple trials may provide important information about the efficacy of a therapy in clinical practice, they are expensive, difficult to coordinate, add variability to the results, and do not provide adequate data for a detailed analysis of the results obtained.

The mortality rate in the patients without gram-negative bacteremia was 41% for the HA-1A group and 37% for the placebo group. The difference in the mortality was 4% and was not statistically significant ($P = 0.134$). The CI for this difference (−0.8% to 8.8%) is a range that includes no difference in mortality between the two groups. Evaluation of the adverse events reported in patients given placebo and those treated with HA-1A did not identify any previously unreported reactions attributable to HA-1A.

The safety of HA-1A was assessed in more than 3000 patients who have received the antibody in clinical trials. No adverse events have been reported more frequently with HA-1A than with placebo that might account for the higher mortality rate observed in patients without gram-negative bacteremia. Quezado and associates (9) reported that HA-1A increased the mortality rate in a canine model of endotoxemia. The mechanism by which HA-1A may have caused more deaths in this model is unknown, and the results have not been reproduced. The relevance of this model to the safety of HA-1A treatment in clinical practice is unclear because the data from clinical trials do not indicate any statistically significant excess mortality rate in patients treated with HA-1A.

The design and subsequent results of the first interim analysis of the CHESS trial required that we suspend patient enrollment because the stopping rule for mortality in patients without gram-negative bacteremia was met. The stopping rule required the trial to be suspended if the number of deaths in the HA-1A group exceeded the number of deaths in the placebo group with a P value of less than 0.1 (one-tailed test). The stopping rule was designed to be sensitive and to cause suspension of enrollment if any evidence suggested excess deaths with HA-1A treatment in patients who were not expected to benefit from therapy (those in shock but without gram-negative bacteremia). The level of significance used to stop the trial was greater than that used conventionally in significance tests of differences between treatment groups in a clinical trial.

Conclusions

The results of the CHESS trial do not support use of septic shock as an indication for HA-1A treatment. Other criteria for patient selection are needed to identify patients who are severely ill and dying from endotoxemia. More specific selection criteria might also reduce the proportion of patients without endotoxemia who may receive HA-1A treatment.

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There are men and classes of men that stand above the common herd: the soldier, the sailor, and the shepherd not infrequently; the artist rarely; rarelier still, the clergyman; the physician almost as a rule. He is the flower (such as it is) of our civilization; and when that stage of man is done with, and only to be marvelled at in history, he will be thought to have shared as little as any in the defects of the period, and most notably exhibited the virtues of the race. Generosity he has, such as is possible to those who practise an art, never to those who drive a trade; discretion, tested by a hundred secrets; tact, tried in a thousand embarrassments; and what are more important, Heraclean cheerfulness and courage. So that he brings air and cheer into the sick room, and often enough, though not so often as he wishes, brings healing.

Robert Louis Stevenson
Underwoods

Submitted by:
Ernesto G. Scerpella, MD
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Submissions from readers are welcomed. If the quotation is published, the sender's name will be acknowledged. Please include a complete citation, as done for any reference.—*The Editors*

Pulmonary Function and Gastroesophageal Reflux in Systemic Sclerosis

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■ *Objective:* To determine the relations among esophageal dysfunction, gastroesophageal reflux, and lung involvement in patients with systemic sclerosis.

■ *Design:* Retrospective review of esophageal motility, esophageal pH, and pulmonary function data.

■ *Setting:* University hospital outpatient clinic and community.

■ *Patients:* 39 consecutively referred patients who were grouped according to the presence or absence of abnormal distal (pH <4.0 for >5% of the 24-hour monitoring period) or proximal (pH <4.0 for >1% of the 24-hour period) gastroesophageal acid reflux. Patients were also grouped according to the presence or absence of distal esophageal peristalsis.

■ *Measurements:* Esophageal manometry, dual-probe (distal and proximal) esophageal 24-hour pH measurements, and pulmonary function studies (forced vital capacity, forced expiratory volume at 1 second, total lung capacity, and single-breath carbon monoxide diffusing capacity [D_{LCO}]).

■ *Results:* The mean total lung capacity (values as percentage predicted) was 87.1% ± 11.2% (SD) for patients with abnormal proximal reflux and 77.8% ± 21.6% for patients with normal proximal reflux (difference, 9.3%; 95% CI, −1.4% to 20.0%). The mean forced vital capacity for these patients was 91.1% ± 12.4% and 85.4% ± 25.6%, respectively (difference, 5.7%; CI, −6.9% to 18.1%). The mean total lung capacity was 83.8% ± 15.4% for patients with abnormal distal reflux and 77.9% ± 22.7% for patients with normal distal reflux (difference, 5.9%; CI, −7.6% to 19.4%). Among potential confounders of pulmonary measures, only smoking was related to decreased pulmonary function (smoking related to decreased D_{LCO} $P < 0.01$). Smoking was more common in patients with abnormal distal reflux than in those with normal distal reflux (65% compared with 25%, $P = 0.03$). After adjusting for smoking, the difference in mean D_{LCO} between patients with abnormal compared with normal distal reflux was 7.19% (CI, −8.5% to 22.9%).

■ *Conclusion:* Important measures of lung volume indicative of interstitial lung disease (total lung capacity, forced vital capacity) do not appear to be related to abnormal gastroesophageal acid reflux in patients with systemic sclerosis.

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Progressive systemic sclerosis (scleroderma) is a connective tissue disorder of variable course and unknown cause that can involve the skin, heart, kidneys, lungs, and gastrointestinal tract. Gastrointestinal involvement is predominantly esophageal (1) and, after changes in the skin and peripheral vasculature, is the third most common manifestation of systemic sclerosis (2). Lung involvement, the fourth most common manifestation (3), is currently the chief cause of death in these patients (2). Therapeutic interventions are now available for certain types of visceral involvement; however, no uniformly effective treatment exists for pulmonary involvement in patients with systemic sclerosis.

Abnormal pulmonary function as a consequence of gastroesophageal reflux has been previously suggested (4–14). Pulmonary function may be adversely affected either by microaspiration of refluxed material into the lung or by stimulation of a vagal reflex arc (from the esophagus to the airways) by gastric contents in the lower esophagus. Because patients with systemic sclerosis often have coexisting interstitial lung disease and esophageal disease, manifested by abnormal motility and gastroesophageal reflux, a causal relation between the two has been suggested (12). The existence of similar pathologic findings in the lung and of pulmonary function test alterations in patients with systemic sclerosis and in persons and experimental animals with esophageal and tracheal acid exposure (2–4, 6–8, 11–13, 15–23) has also led some investigators to postulate a link between pulmonary involvement in systemic sclerosis and gastroesophageal reflux (12). If such a causal link were to be shown, aggressive treatment of gastroesophageal reflux might decrease the morbidity and mortality caused by lung involvement in patients with systemic sclerosis. We studied the relations among esophageal dysfunction, gastroesophageal reflux, and pulmonary function in patients with systemic sclerosis to determine if gastroesophageal reflux could be the cause of interstitial lung disease in these patients.

Methods

Patients

The records of 47 consecutive patients with systemic sclerosis who were seen at Thomas Jefferson University Hospital between October 1989 and August 1991 were reviewed. Of the 47 patients, 39 completed tests of pulmonary function, esophageal

Abbreviation	
D_{LCO}	Single-breath carbon monoxide diffusing capacity

